Submitting an IND: What You Need to Know

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Topics

1. IND Application: Content and Format
2. IND Submission: The First 30 Days
3. Responsibilities of Sponsors and Investigators
4. IND Amendments
5. Reporting Requirements
6. Inactivation; Reactivation; Withdrawal; Termination

IND Application: Content and Format

Content

- Requirements outlined in **21 CFR 312.23**
  - Cover Letter
  - Form FDA 1571
  - Form FDA 3674
  - Table of Contents
  - Introductory Statement/General Investigational Plan
  - Investigator's Brochure

IND Application: Content and Format

- Nonclinical
  - Sufficient data to support clinical protocol
  - Basic exposure data
- Chemistry, manufacturing, and controls
  - Sufficient information to assure proper identification, quality, purity, and strength
  - Sufficient information to assess whether batches can be adequately produced and consistently supplied

IND Application: Content and Format

- Clinical protocol
  - Determine the phase of development
  - Provide supporting data (e.g., from ex-U.S. trials, PK data)
  - Specify how to ensure safety of the subjects/patients in the study (#1 reason INDs are placed on clinical hold)

IND Application: Content and Format

- Bundling: One IND or More?
  - One IND:
    - Early development studies - not sure of indication or dosage form
    - Closely related indications within a single review division
    - Multiple, closely-related routes of administration using same dosage formulation
    - Combination of two or more investigational new drugs for concomitant use

IND Application: Content and Format

- Bundling: One IND or More?
  - Multiple INDs:
    - Two or more unrelated conditions being developed
    - Multiple dosage forms being extensively investigated
    - Multiple routes of administration being extensively investigated

IND Application: Content and Format

Format

- Paper
  - Common Technical Document (CTD) format
  - Regulatory format (21 CFR 312.23)
- Electronic
  - Must use CTD format
  - Physical media
  - Electronic Submissions Gateway (ESG)

IND Application: Content and Format

Mailing address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

No user fee required!

IND Application: Resources

How Drugs are Developed and Approved:

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm

IND Application (includes links to all IND guidances):

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm

Small Business Assistance: FAQs on Drug Development and INDs

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069898.htm

CTD Format Guidances:

- http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065006.htm

IND Application: Resources

Electronic Submissions:

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm
- Preparation questions: esub@cder.fda.gov

Electronic Submissions Gateway:

- http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm
- Preparation/Registration/Policy Questions: esgprep@fda.hhs.gov
- Technical Issues: esgreg@gnsi.com

Secure e-mail account:

- Contact Wendy Lee at: wendy.lee@fda.hhs.gov

Pre-assigned application number:

- Send one email per application number request to cderappnumrequest@fda.hhs.gov.

IND Submission: The First 30 Days

- IND arrives in the Central Document Room
  - If electronic: Loaded into the EDR(Electronic Document Room)
  - If paper: Sent to White Oak Document Room
  - Data entered into DARRTS (Document Archiving, Reporting, and Regulatory Tracking System)
  - Review division's Chief, Project Management Staff (CPMS) notified

IND Submission: The First 30 Days

- Regulatory Project Manager (RPM) assigned
  - Your point of contact with the review division
  - Issues IND Acknowledgement letter (includes IND number; receipt date; address for future submissions; contact information)
  - Performs regulatory/administrative review of IND application for completeness
  - Tracks/manages IND review process

IND Submission: The First 30 Days

- Scientific Discipline Team Leaders notified and reviewers assigned
  - Clinical
  - Nonclinical pharmacology/toxicology
  - Chemistry
  - Clinical pharmacology
  - Biostatistics (if phase 3 protocol)
  - Consult reviewers as needed

IND Submission: The First 30 Days

- Safety Review
  - The review division will determine within **30 days** of receipt of your IND whether your study is “reasonably safe to proceed” (active) or will be placed on clinical hold
  - Some review divisions may issue a “safe to proceed” letter; Otherwise, “No news is good news”
  - INDs are not approved

IND Submission: Clinical Hold

- Clinical Hold: [21 CFR 312.42(a)]
  - An order issued by FDA to the sponsor of an IND to delay a proposed clinical investigation or suspend an ongoing clinical investigation
    - Full Clinical Hold: A delay or suspension of all clinical study under an IND.
    - Partial Clinical Hold: A delay or suspension of only part of the clinical study under an IND (e.g., a specific protocol or part of a protocol is allowed to proceed).

IND Submission: Clinical Hold

- Grounds for imposing a clinical hold for phase I trials: [21 CFR 312.42(b)(1)]
  - Human subjects would be exposed to an unreasonable and significant risk of illness or injury
  - Clinical investigators are unqualified
  - Investigator Brochure is misleading, erroneous, or incomplete
  - Insufficient information to assess risks to subjects
  - Exclusion by gender for life-threatening disease

IND Submission: Clinical Hold

- Grounds for imposing a clinical hold for phase 2/3 trials: [21 CFR 312.42(b)(2)]

  – All the reasons listed for phase 1 trials
  – The protocol is deficient in design to meet its stated objectives

IND Submission: Clinical Hold

- If a deficiency is identified that may be grounds for imposing a clinical hold:
  - The review division will attempt to discuss and satisfactorily resolve the matter with you first
  - Many potential holds can be resolved through such discussion (e.g., inadequate patient monitoring)

IND Submission: Clinical Hold

- If a clinical hold is imposed:
  - The review division will notify you by telephone and briefly discuss the clinical hold issues
  - A letter will follow detailing the hold issues and what you must do to resolve them

IND Submission: Clinical Hold

- Your response to the clinical hold letter:
  - Should be complete (i.e., address all the deficiencies identified in the letter)
  - If complete, you will receive an acknowledgement letter
  - If not complete, RPM will notify you

IND Submission: Clinical Hold

- Review division will respond within **30 days** of receipt of your response by either:
  - Removing the clinical hold;
  - Continuing the clinical hold; or
  - Modifying the clinical hold (e.g., full to partial)
- If review team cannot meet the 30-day deadline:
  - Review division will call you and discuss review progress/what is being done to facilitate completion of the review

Sponsor Responsibilities

- General responsibilities [21 CFR 312.50]
  - Select qualified investigators
  - Provide investigators with pertinent information
  - Ensure proper monitoring
  - Ensure that the investigation is conducted according to the general investigational plan/protocol
  - Inform FDA and investigators of significant new adverse effects/risks

Sponsor Responsibilities (cont.)

- Selecting investigators and monitors [21 CFR 312.53]
  - Select investigators that are qualified by training and experience
    - Obtain statement of qualifications (CV) from investigators
    - Should not use disqualified/debarred individuals
      (Debarment list: http://www.fda.gov/ora/compliance.ref/debar/default.htm)
  - Obtain additional information from investigators
    - Signed Form FDA 1572
    - Clinical protocol to be conducted
    - Financial disclosure [21 CFR 54]

Sponsor Responsibilities (cont.)

- Informing investigators [21 CFR 312.55]
  - Provide Investigator's Brochure
    - Description of drug formulation
    - Pharm/tox effects and PK/PD information in animals and humans
    - Possible risks and side effects
    - Precautions/special monitoring
  - Provide new information regarding adverse events and safe use

Sponsor Responsibilities (cont.)

- Review of ongoing investigations [21 CFR 312.56]
  - Monitor the progress of all investigations
  - Review and evaluate evidence of safety and effectiveness of the investigational drug
  - Submit reports to FDA re: safety and progress
  - Assure compliance of investigators
  - Discontinue investigation if drug presents an unreasonable and significant risk (notify FDA, IRB, investigators)

Sponsor Responsibilities (cont.)

- Recordkeeping and record retention [21 CFR 312.57]
  - Receipt, shipment, and disposition of the investigational drug
  - Financial interest paid to investigators
  - Retain records for two years after drug approved OR investigations are discontinued

Sponsor Responsibilities (cont.)

- Permit FDA inspection of records and reports [21 CFR 312.58]
  - Permit inspection of records and reports related to the clinical investigations upon request
  - Provide copies of records and reports upon written request
- Disposition of unused drug [21 CFR 312.59]
  - Assure return of all unused supplies of the investigational drug
  - Ensure safe disposition (does not expose humans to risks)

Transfer of Responsibilities

- You may transfer any or all of your responsibilities to a contract research organization (CRO) [21 CFR 312.52]
  - Inform FDA in writing specifying which responsibilities are being transferred
  - CRO must comply with all applicable regulations associated with the transferred responsibilities

Investigator Responsibilities

- General responsibilities [21 CFR 312.60]
  - Ensure that the investigation is conducted according to the protocol and applicable regulations
  - Protect the rights, safety, and welfare of subjects

- Control of the investigational drug [21 CFR 312.61]
  - Administer drug only to subjects
  - Do not supply the drug to anyone not authorized to receive it

Investigator Responsibilities (cont.)

- Recordkeeping and record retention [21 CFR 312.62]
  - Case histories [e.g., Case Report Forms (CRFs) and supporting data, signed and dated consent forms, medical records]
  - Disposition of the investigational drug (i.e. dates, quantity, and use by subjects)
  - Retain records for 2 years after drug is approved for the indication being investigated or 2 years after the investigation is discontinued

Investigator Responsibilities (cont.)

- Investigator reports to the sponsor [21 CFR 312.64]
  - Progress reports
  - Safety reports
  - Final report
  - Financial disclosure reports
- Assurance of IRB review [21 CFR 312.66]
  - Assure that an IRB is responsible for review and approval of the protocol
  - Report any unanticipated problems involving risk to subjects
  - Not make any protocol changes without IRB approval except to eliminate immediate hazards to subjects

Investigator Responsibilities (cont.)

- Permitting FDA inspection of records and reports [21 CFR 312.68]

- Handling of controlled substances [21 CFR 312.69]
  - Securely locked; limited access

IND Amendments

- Protocol amendments [21 CFR 312.30]
- Information amendments [21 CFR 312.31]

Protocol Amendments

- New Protocol [21 CFR 312.30(a)]
- Changes in Protocol [21 CFR 312.30(b)]
- New Investigator [21 CFR 312.30(c)]

New Protocol [21 CFR 312.30(a)]

- New study may begin provided:
  - Submitted to IND
  - Approved by IRB
- Content and format
  - Copy of the protocol
  - Significant differences from previous protocols
  - Prominent identification (cover letter; form 1571)
  - Reference to any relevant information in IND
  - Request for comment (optional)

Changes in Protocol [21 CFR 312.30(b)]

- Amendment required for:
  - Phase 1: Change significantly affecting subject safety
  - Phase 2/3: Changes significantly affecting safety, scope, scientific quality

Changes in Protocol (cont.)

- Protocol changes may be implemented provided:
  - Change submitted to IND
  - Approved by IRB
- Exception: Change to eliminate an apparent immediate hazard to subjects can be implemented immediately.

Changes in Protocol (cont.)

- Content and Format
  - Description of the change
  - Reference to original protocol submission
  - Prominent identification (cover letter; form 1571)
  - Reference to any relevant information in IND
  - Request for comment (optional)

New Investigator [21 CFR 312.30(c)]

- An amendment is required when a new investigator is added to an ongoing study
  - Exception: adding a licensed practitioner to a treatment IND/treatment protocol
- Submit within 30 days of the new investigator being added
- Grouping several new investigators in one submission is permitted

New Investigator (cont.)

- Content and Format
  - Name and qualifications
  - Reference to previously submitted protocol
  - Prominent identification (cover letter; form 1571)
  - Additional info required under 21 CFR 312.23(a)(6)(iii)(b)

Information Amendments

[21 CFR 312.31]

- Amendment required for submission of essential information not within scope of protocol amendment, safety report, annual report
  - New information (e.g., clinical, clinical pharmacology, nonclinical; chemistry, study reports)
  - Discontinuance of study (within 5 days of decision)

Information Amendments (cont.)

- Submit as necessary (but to the extent possible, no more than every 30 days)
- Content and Format
  - Prominent identification (cover letter; form 1571)
  - Statement of nature and purpose
  - Organized in format appropriate for scientific review
  - Request for comment (optional)

IND Reporting Requirements

- Safety Reports [21 CFR 312.32]
- Annual Reports [21 CFR 312.33]

Safety Reports: Definitions

[21 CFR 312.32(a)]

- Associated with the use of the drug: reasonable possibility of causality
- Disability: substantial disruption of ability to conduct normal life functions
- Life-threatening adverse drug experience (ADE): immediate risk of death (based on investigator's judgment)
- Serious ADE: any dose resulting in death; life-threatening ADE; hospitalization/prolonged hospitalization; disability; congenital anomaly/birth defect; medical event requiring medical/surgical intervention
- Unexpected ADE: specificity/severity inconsistent with known safety profile

Review of Safety Information

[21 CFR 312.32(b)]

- Review all information relevant to the safety of the drug from all sources (foreign and domestic) including:
  - Clinical, epidemiological, and animal investigations
  - Commercial marketing experience
  - Scientific literature reports
  - Unpublished scientific papers
  - Reports from foreign regulatory authorities

Types of Safety Reports

- Written 15-day reports
- Telephone/fax 7-day reports
- Follow-up reports

Written Safety Reports

[21 CFR 312.32(c)(1)]

- Notify FDA in writing of:
  - Any ADE associated with the use of the drug that is both **serious and unexpected**
  - Any finding from tests in lab animals that suggests significant risks for human subjects
- When?
  - ASAP; NO LATER THAN **15 days** after receipt of information

Written Safety Reports (cont.)

- Content and Format
  - FDA Form 3500A (MedWatch) or narrative format identified as **"IND Safety Report"**
  - Reference previous, similar reports
  - Analyze the significance of the ADE in light of similar adverse events

Telephone/Fax Safety Reports

[21 CFR 312.32(c)(2)]

- Notify FDA by telephone or fax of:
  - Any unexpected **fatal or life-threatening** ADE associated with the use of the drug
- When?
  - ASAP; NO LATER THAN **7 days** after sponsor's receipt of information

Follow-up Safety Reports

[21 CFR 312.32(d)]

- Submit all relevant follow-up info ASAP

- Missed reports (not initially determined to be reportable): Submit ASAP but NO LATER THAN **15 days** from discovery

Safety Reports: Miscellaneous

- Variations [21 CFR 312.32(c)(3)]
  - FDA may request varying frequency and format: Sponsor/FDA agreement
- Results of investigation of other safety information that does not fall under the specific reporting categories are submitted via:
  - Information amendment
  - Annual Report
- Disclaimer [21 CFR 312.32(e)]: You need not admit, and may deny, that the safety report constitutes an admission that the drug caused or contributed to the ADE

Annual Report [21 CFR 312.33]

Report of the progress of the investigation that includes:

- Individual study information
  - Title, purpose, patient population, study status
  - Total # of subjects planned, #entered to date, by age group, gender, and race; the #completed as planned, #drop-outs
  - Study results, if completed

Annual Report (cont.)

- Summary Information
  - Most frequent and most serious ADEs by body system
  - Summary of all IND safety reports submitted during past year
  - Study drop-outs due to ADEs
  - Subjects who died during study; cause of death
  - New info re drug's actions
  - Completed nonclinical studies; summary of major findings
  - CMC changes

Annual Report (cont.)

- General investigational plan for coming year
- Revisions to the Investigator Brochure
- Phase 1 study modifications not previously reported
- Significant foreign marketing developments
- Log of outstanding business (optional)

Annual Report (cont.)

- Must be submitted within 60 days of the “in effect” anniversary date

- May request bundled annual reports/waiver of anniversary date
  - Multiple applications for the same active moiety
  - Harmonize and consolidate annual report

Inactivation [21 CFR 312.45]

- You or FDA may initiate inactivation if:
  - No subjects entered into studies for ≥2 years
  - All investigations on clinical hold for ≥1 year

- If FDA initiates inactivation:
  - Pre-inactivation letter issued to you
  - You have **30 days** to respond

Inactivation (cont.)

- If IND inactivated:
  - All investigators notified
  - Stocks of drug returned to you or disposed of properly
  - **Annual reports need not be submitted**

Reactivation [21 CFR 312.45(d)]

- If you intend to resume clinical investigations under an inactive IND, you must submit a protocol amendment that includes:
  - Proposed general investigational plan
  - Appropriate protocol(s)
  - Additional information supporting the protocol(s)
  - Reference previously submitted information
- Safety review
  - The review division will determine whether your reactivated IND is safe to proceed or will be placed on clinical hold within **30 days** of receipt of your protocol amendment

Withdrawal [21 CFR 312.38]

- You may withdraw an IND at any time
  - Notify FDA
  - All investigations end
  - All current investigators notified
  - All stocks of the drug returned to you
- If IND is withdrawn due to safety reasons:
  - All of the above plus:
    - Notify reviewing IRBs
    - Reasons for the withdrawal

Termination [21 CFR 312.44]

- FDA may terminate an IND based on:
  - Deficiencies in the IND
  - Conduct of an investigation
  - An IND that remains on inactive status for ≥5 years (21 CFR 312.45)
- Pre-termination letter issued: allows you 30 days to respond to our proposal to terminate except where there is immediate and substantial danger to health of individuals

Questions?

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